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Asymmetric organocatalytic cascade Michael/hemiketalization/retro-Henry reaction of β,γ-unsaturated ketoesters with α-nitroketones†

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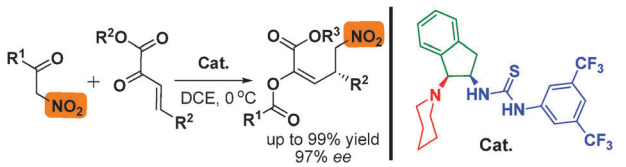
An unprecedented enantioselective organocatalytic Michael/hemiketalization/retro-Henry cascade sequence is described, which catalyzed by a simple bifunctional indane amine-thiourea catalyst. This process provides a new route to the enantioselective synthesis of 5-nitro-pent-2-enoates, a precursor to α-ketolactam.

The synthesis of enantiopure molecules still remains as a challenging talk in organic synthesis.[1] Organocatalysis, one of the most powerful synthetic tools, has attracted much attention and achieved great advances in this area for the past decades.[2] Among the organocatalytic reaction modes, bifunctional Brønsted-base thiourea catalysis has proven its ability and diversity in wide range of reactions, notably Michael addition reactions that allowed the formation of new C–C bonds. Recently, a large number of Michael addition reactions triggered cascade reactions have been reported *via* the mode of bifunctional Brønsted-base thiourea catalysis.[3] In particular, these cascade reactions efficiently assembled many interesting natural molecules and synthetic useful intermediates in a one-pot process.[4]

In organic synthesis, the utilization of various carbonyl compounds is commonplace as they enable diverse C–C bond formation reactions. The use of β,γ-unsaturated ketoesters is not as widespread and their reactivity has rarely been investigated despite their functionality, which offers a useful starting point for additional transformations.[5] Therefore, β,γ-unsaturated ketoesters represent a group of interesting synthetic building blocks for future study. Herein, we document an asymmetric organocatalytic cascade Michael/hemiketalization/retro-Henry reaction of β,γ-unsaturated ketoesters with α-substituted ketones catalyzed by a bifunctional indane amine-thiourea catalyst that can lead to high yield and good to excellent enantioselectivity [eqn (1)].



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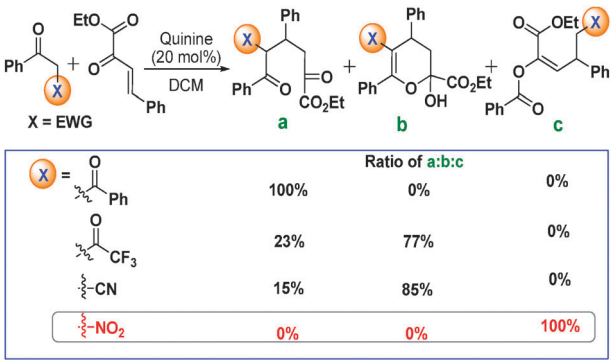
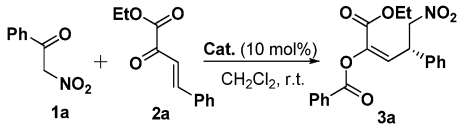


Scheme 1 Investigation of α-substituted ketones.

We began our investigation by examining the organic base catalyzed reaction of α- substituted ketones with β,γ-unsaturated ketoesters. The initial experiment showed that the use of a catalytic amount of quinine enabled a reaction between 1,3-diphenyl-1,3-propanedione and (*Z*)-ethyl 2-oxo-4-phenylbut-3-enoate that resulted in the formation of Michael adduct **a** (Scheme 1). However, if stronger electron withdrawing groups were introduced to acetophenone, a mixture of Michael adduct **a** and its anomer form **b** were generated (Scheme 1, a : b = 23 : 77, 15 : 85, respectively). Further investigation showed the only formation of compound **c** without the formation of both the Michael adduct **a** and its anomer form **b** when the cyano group was replaced by a nitro moiety in the α-substituted ketones (Scheme 1). It is noteworthy that compound **c** is the precursor of δ-amino α-keto acid or cyclic α-keto lactam which bears a chiral center at the γ-position.

On the basis of these observations we decided to develop an asymmetric version of this cascade Michael/hemiketalization/retro-Henry reaction using the catalysts developed from our laboratory. Following our previous investigations on bifunctional indane amine-thiourea promoted transformations,[6] we reasoned that it is feasible to activate β,γ-unsaturated ketoester using the amine group and thiourea group through the enolization and H-bonding formation. The initial experiments showed that the reaction of **1a** with β,γ-unsaturated ketoester **2a** could be carried out in the presence of catalysts **Ia–c** in CH_2Cl_2 to give the corresponding 5-nitro-pent-2-enoate **3a** in high yields and good enantioselectivities (Table 1, entries 1–3, 90–93% yield, 77–85% *ee*). However, poor performance demonstrated by catalysts **IIa–b** inferred that switching the position between tertiary amine group and thiourea group

Table 1 Evaluation of indane bifunctional thiourea organocatalysts[a]



Entry	Cat.	Yield (%)[b]	*ee* (%)[c]
1	**I-a**	**92**	**−84**
2	**I-b**	90	−77
3	**I-c**	**93**	**−85**
4	**II-a**	93	−36
5	**II-b**	94	−27
6	**III**	93	−66
7	**IV**	**94**	**85**

[a] Reaction was conducted on 0.1 mmol scale in CH_2Cl_2 (0.5 mL) at r.t. for 6 h, and the ratio of **1a**/**2a** is 1 : 1.1. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (*ee*) was determined by HPLC.

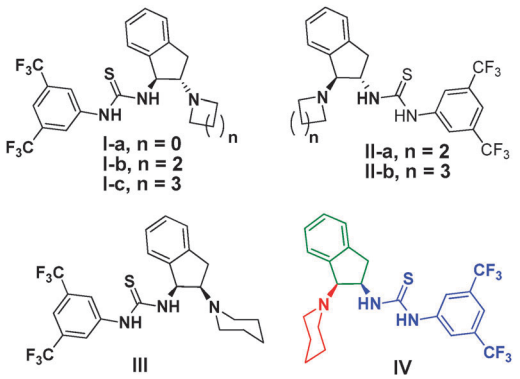


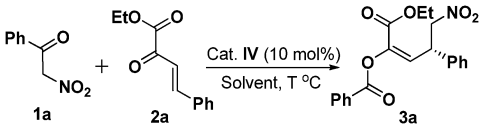
Fig. 1 Evaluated bifunctional indane thiourea organocatalysts.

could dramatically affect the catalytic performance for this reaction (Table 1, entries 4 and 5, 36% and 27% *ee*, respectively). Meanwhile, catalyst **III** was synthesized and investigated. In contrast to catalyst **Ic**, catalyst **III** has a chiral center inversion on tertiary amine (Fig. 1). Indeed, catalyst **III** demonstrated a better enantioselectivity than catalysts **IIa–b** (Table 1, entry 6, 93% yield, 66% *ee*). Catalyst **IV** was synthesized in the later stage and it was derived from catalyst **III** *via* a switch between tertiary amine and thiourea groups. Surprisingly, with regard to the 3-dimensional structure of the desired product, catalyst **IV** favored another enantiomer with a 85% *ee* (Table 1, entry 7). Based on observation, we believed that catalyst **Ic** and **IV** can both give excellent enantioselectivity control and generate *R* and *S* enantiomers equally (Table 1, entries 3 and 7, −85% *ee* and 85% *ee*).

Further reaction optimization focused on the solvent and reaction temperature in the presence of catalyst **IV** (Table 2). These experiments revealed that the best results with regard to yield and enantioselectivity were obtained in DCE at 0 °C (Table 2, entry 11). The process completed within 24 h and gave 5-nitro-pent-2-enoate **3a** in 95% yield and 92% *ee*. Further decrease in temperature did not show any significant improvement on enantioselectivity (Table 2, entry 12, 48 h, 92% *ee*).

Using the optimized reaction conditions we investigated the scope of the bifunctional indane amine-thiourea **IV** catalyzed cascade Michael/hemiketalization/retro-Henry reaction

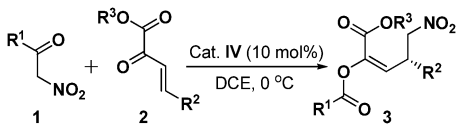
Table 2 Optimization of reaction conditions[a]



Entry	Solvent	*T*/°C	*t*/h	Yield (%)[b]	*ee* (%)[c]
1	DMSO	r.t.	6	85	2
2	DCE	r.t.	6	95	87
3	$CHCl_3$	r.t.	6	93	75
4	CH_2Cl_2	r.t.	6	94	85
5	Anisole	r.t.	6	95	81
7	Et_2O	r.t.	6	94	56
8	Toluene	r.t.	6	95	65
9	Xylene	r.t.	6	94	64
10	$PhCF_3$	r.t.	6	95	77
11	**DCE**	**0**	**24**	**95**	**92**
12	DCE	−20	48	92	92

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (*ee*) was determined by HPLC.

Table 3 Substrate scope[a]



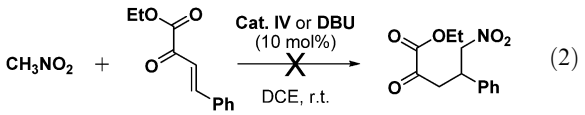
Entry	R^1	R^2	R^3	*t*/h	Yield (%)[b]	*ee* (%)[c]
1	Ph	Ph (**3a**)	Et	24	95	92
2	Ph	4-FC_6H_4 (**3b**)	Et	24	96	90
3	Ph	4-ClC_6H_4 (**3c**)	Et	24	97	90
4	Ph	2-ClC_6H_4 (**3d**)	Et	24	99	97
5	Ph	2-BrC_6H_4 (**3e**)	Et	24	97	96
6	Ph	4-$MeOC_6H_4$ (**3f**)	Et	24	93	93
7	Ph	4-$MeSC_6H_4$ (**3g**)	Et	24	98	91
8	Ph	4-allyloxyC_6H_4 (**3h**)	Et	36	96	93
9	Ph	4-$BnOC_6H_4$ (**3i**)	Et	36	95	93
10	Ph	4-*i*PrC_6H_4 (**3j**)	Et	36	97	92
11	Ph	2-MeC_6H_4 (**3k**)	Et	36	90	92
12	Ph	1-Naphthyl (**3l**)	Et	36	97	94
13	Ph	2-Thiophene (**3m**)	Et	36	90	91
14	Ph	Et (**3n**)	Et	36	93	92
15	Ph	Ph (**3o**)	Me	24	96	92
16	4-ClC_6H_4	Ph (**3p**)	Et	24	97	90
17	4-$MeOC_6H_4$	Ph (**3q**)	Et	36	98	94
18	4-*i*PrC_6H_4	Ph (**3r**)	Et	36	96	92
19	2-Thiophene	Ph (**3s**)	Et	36	90	90
20	*n*-Propyl	Ph (**3t**)	Et	36	91	75

[a] Unless specified, see the Experimental section for reaction conditions. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess (*ee*) was determined by HPLC.

employing various β,γ-unsaturated ketoesters **3** (Table 3). In general, various β,γ-unsaturated ketoesters could be employed in this transformation. A set of 5-nitro-pent-2-enoates **3a–o** was isolated in high yields (90–99%) and with excellent enantioselectivities (90–97% *ee*). Aromatic γ,β-unsaturated ketoesters having both electron-withdrawing (Table 3, entries 2–5) and electron-donating substituents (Table 3, entries 6–11) can effectively be used in this reaction; the substitution pattern of arene had no obvious influence on

the enantioselectivity of this transformation (Table 3, entries 2–7). Additionally, it was possible to use both heteroaromatic (Table 3, entry 13) and aliphatic β,γ-unsaturated ketoester (Table 3, entry 14) in this reaction. Furthermore, various α-nitro ketones were used in this reaction and 5-nitro-pent-2-enoates **3p–t** were generated in high yields (Table 3, entries 16–20, 90–98%) and good to excellent enantioselectivities (75–94% *ee*).

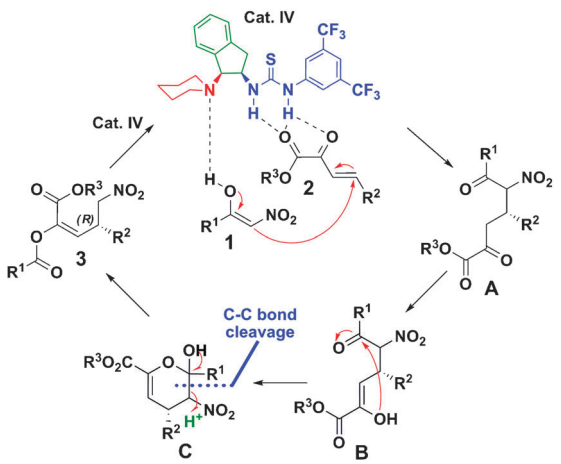
Two additional experiments had been examined using nitromethane instead of α-nitro ketone **1a** to react with β,γ-unsaturated ketoester **2a** in the presence of catalyst **IV** or a strong base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [eqn (2)]. However, no desired products were obtained in both two experiments.



(2)

With regard to the mechanism, we deduce that the intermediary Michael adduct **A** is generated from the reaction of β,γ-unsaturated ketoester **2** and α-nitro ketone **1** (Scheme 2). Subsequently, enolization to intermediate **B** followed by a hemiketal cyclization gives rise to adduct **C**. Adduct **C** then undergoes a retro-Henry reaction to afford the desired product **3** with the regeneration of catalyst **IV**. The constitution and absolute configuration of the new products were determined by X-ray crystal structure analysis of a suitable single crystal (**3u**) (Fig. 2) (see ESI†).

In summary, we have developed a new enantioselective bifunctional indane amine-thiourea catalyzed cascade Michael/hemiketalization/retro-Henry reaction of β,γ-unsaturated ketoesters with α-substituted ketones. Further investigations on the



Scheme 2 Indane amine-thiourea catalyzed Michael/hemiketalization-/retro-Henry reaction of β,γ-unsaturated ketoester **2** with α-nitro ketone **1**.

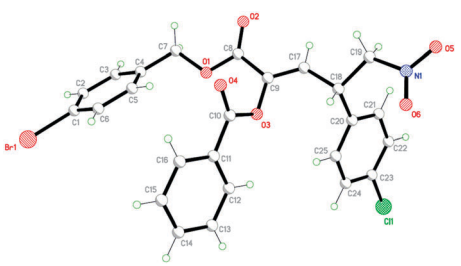


Fig. 2 X-Ray crystal structure of 5-nitro-pent-2-enoate **3u**.

applications of chiral 5-nitro-pent-2-enoates for the development of synthetic useful scaffolds are currently underway.

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